March 2, 2001

The Food and Drug Administration is pleased to comment on the Draft Interim Guidance on "Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection."

Overall Concern

The agency agrees that it is critically important for financial interests to be managed or eliminated. We are concerned, however, that the draft guidance places too great a responsibility on the IRBs. This responsibility should not be placed on IRBs—which are already over-burdened and are not appropriately constituted to perform this task. This responsibility would further over-burden IRBs, and distract from their core function, which is to protect human subjects. In addition, as currently constituted, IRBs may not be able to fulfill this requirement well. The document should explicitly address these concerns to ensure that IRBs are not given the primary responsibility for managing financial interests.

According to the preamble to the guidance document, the HHS Inspector General found that one-quarter of IRBs (it contacted?) reviewed to varying degrees financial arrangements between investigators and research sponsors. The guidance document, however, describes a far greater level of effort in the review of financial interests than is currently done by the majority, if not all, of these IRBs. We believe that a different committee (conflict of interest committee (COIC) or equivalent) should be responsible for the review, management, or elimination of financial interests. The only additional responsibility that should be placed on the IRB would be to receive the final action of the COIC. The receipt of that information would be to solely allow the IRB to determine if they need to take some further action, for example, add information to the consent form or place further restrictions on the study. The IRB should also be able to request any further information it needs from the COIC.

Specific Comments

It is not clear whether the preamble to the interim guidance will remain with the rest of the guidance document. Thus, we have provided comments on the preamble language as well as on the guidance itself.

Preamble

- Page 1, 2nd paragraph
  - 2nd sentence: As written, it sounds as though IRBs are "considering" making financial arrangements "with sponsors of research" (that is, they are seeking money). It is also doubtful that the HHS Inspector General contacted all IRBs and was therefore able to conclude what "one-quarter of IRBs" were doing. For the first concern, we suggest modifying the sentence to read "...of IRBs it contacted are reviewing financial arrangements between clinical investigators and research sponsors to varying...." For the latter concern, we suggest either

modifying the phrase "one-quarter of IRBs" with "it contacted" or including the number of IRBs contacted and the number that reviewed financial arrangements.
  - Last sentence, last line: We believe this should be changed to read: "...management **of financial interests** and resolution of conflicts."
- Page 1, 3rd paragraph: The first two sentences appear to conflict with the conclusion in the third sentence. Further, they contain dated material (e.g., "At this time"; "Recent issues of the NEJM"). We believe that the third sentence could stand alone and suggest that the first two sentences be deleted.
- Page 1, 4th paragraph: Whenever possible we believe that it would be better to avoid the phrase "conflicts of interest." Thus, we suggest modifying this sentence to read "...in their deliberations concerning **financial** interests, and to facilitate...."
- Page 2, 2nd paragraph
  - 1st sentence: This sentence suggests that NIH, CDC, FDA, AHRQ, HRSA, IHS, etc. have regulations, policies, and guidance on financial conflict of interest and financial disclosure in effect that were previously described. However, only the PHS regulations regarding financial conflict of interest and FDA regulations on financial disclosure are discussed. If there are other regulations, policies, and guidance covering these issues by other federal agencies that may be helpful, these should be discussed and made available. If other agencies do not have such documents, then they should be deleted from the list. If the agencies are retained on the list without further discussion of their documents, then "As above..." should be deleted and their acronyms spelled out.
  - 2nd sentence: This sentence would be clearer if it were to read "...modify any **existing regulation, policy, or guidance. Rather it is intended** to help IRBs, clinical investigators, and institutions in carrying out their responsibilities...in research that they **conduct** under the 'Common Rule' **or** the equivalent...."
- Page 2, 3rd paragraph
  - 1st sentence: We suggest deleting this sentence; it is not needed.
  - 2nd sentence: To make this easier to read, we suggest modifying it to read "Some policies and...requirements are in place, some with thresholds for reporting...holdings. **However,** there is no consensus **on** the nature...."
  - 3rd sentence: Again, for ease in reading, we suggest changing this to read "In fact, FDA does not...by investigators (through the sponsor) **in** FDA-regulated research."
  - 4th and 5th sentences: As written, these place the main responsibility on the IRB. As previously discussed, we believe that this should not be an IRB responsibility. Suggest rewriting the 4th sentence to read: "This document emphasizes financial...issues that, hopefully, will facilitate informed unbiased discussion and properly informed research subjects. We recommend that the last (5th) sentence be deleted.
- Page 2, 4th paragraph
  - 1st sentence: This would be easier to read if it were not in the passive voice. Suggest rewriting to read "**If** sponsor...and investigators **clearly demonstrate** to potential subjects...be eliminated, **a** stronger bond of trust **can develop** that can facilitate enrollment..."

Interim Guidance

1. the Institution: Institutional Considerations

- 1.1, 1st paragraph: This paragraph references "significant financial interest." Elsewhere in the document "significant" is not used. There is also no guidance on how to assess what is significant. It may be helpful to provide some guidance on this issue if the current phrase is retained. For individuals not familiar with the PHS regulations, this paragraph may cause confusion. For example, who may serve as a "designated Institutional official"? To what regulations does "Under the regulations…" refer? Who is going to collect the conflict of interest information from the investigator? It may be better to put the information that is currently in this paragraph in a footnote. Otherwise, further clarification would be helpful.
- 1.1, 2nd paragraph
  - 1st sentence: Is it true that "Many" institutions have a Conflict of Interest Committee (COIC) or only "Some"? (Note earlier comments about the HHS Inspector General findings.) Further, it may be helpful if the guidance described several examples of oversight committees, but used one type of oversight committee (the Conflict of Interest Committee) throughout the guidance document. Various terms are currently used throughout the document to describe oversight—sometimes "Institutional Official" or "equivalent body" or "Conflict of Interest Committee"—the use of one term would add clarity.
  - 2nd sentence: Suggest rewriting for clarity as follows "**A COIC** is useful to an institution; **it keeps** the IRB from bearing the burden…."
  - 3rd sentence: Suggest rewriting for clarity as follows: "The chair of **the COIC** generally shares the results of the COIC reviews that relate to specific problematic protocols with the IRB Chair/Staff **and the designated Institutional official.**"
  - 4th sentence: This might be clearer if it read "The IRB should be aware of how the Conflict of Interest Committee defines potential or actual financial conflicts of interest including how they are managed, reduced, or eliminated."
  - 5th sentence: Recommend that this be deleted. If the "institution" rather than the COIC is dealing with financial interests (that is, sharing how it dealt with the investigator in terms of the financial interest with the COIC) then it is unclear what the role of the COIC is. Further, in order to minimize the workload on the IRB, only limited information should be shared with it. Perhaps the COIC is to serve as the "designated Institutional official." If that is the case, it should be stated.
- 1.2, 1st paragraph
  - 1st sentence: We suggest that it might be more appropriate for this information to go to the COIC rather than to the institutional official—or that the COIC be indicated as an option. We suggest that you also consider adding a regulatory citation for FDA's regulation (21 CFR 54).
  - 2nd sentence: It is not clear when, if ever, it would be "appropriate" to share information from the form 3454 or 3455 with the IRB. We therefore recommend that the last phrase ("and, if appropriate, the IRB") be deleted.
- 1.2, 2nd paragraph: The letter concerning significant financial conflict of interest should be shared with the COIC, not the IRB.

- 1.3: The same concerns described in this section could also apply to the COIC. Thus, this paragraph should include COIC in each place that "IRB" is used.
- 1.4
  - 1st sentence: It is not clear why "IRB staff" should disclose their financial interests and, yet, not be included in many other sections of this guidance. If "IRB staff" is to remain, the rationale should be described. Further, if IRB staff are included, why would other "key research personnel" not be included? The guidance should clarify who is included. If all key personnel are subject to this guidance, then they should be identified consistently throughout.
  - 2nd sentence: It is not clear what "all of the above" refers to. Is this intended to refer to IRB staff, chair, and all members, or is it also to include clinical investigators? Listing the parties would add clarity.
- 1.5
  - 1st sentence: We suggest adding "key research staff and COIC members" in the list of individuals who should be educated. We also recommend that "financial conflict of interest" be changed to "financial interest" in both this sentence as well as the one that follows.
  - indented paragraph or footnote (depending on version): It should be noted that the RCR educational policy has been suspended.
- 1.6
  - Throughout this section "conflicts of interest" should be changed to "financial interest".
  - Last sentence: This is difficult to read. Suggest that it be shortened and in the next to the last line changed to read "…or **by having it** carried out…"
- 1.7: We believe that the parenthetical phrase should read "(**independent** conflicts of interest committee)."
- 1.8, 1st sentence: Again, we believe that the financial relationships should be submitted to the COIC rather than to the "Chair/Staff of the IRB."

2. *Clinical Investigators*

- 2.1
  - 4th sentence: For clarity, change to read "Additionally, so-called 'recruitment bonuses'…" The complete sentence might be clearer if it were to read: "Additionally, recruitment bonuses, accrual bonuses, and finders' fees for referral of potential participants might entice investigators to under report adverse reactions or influence a positive analysis and interpretation of the research data."
  - Last sentence: It is not clear what is meant by "commitments of financial support unrelated to the study." This should be deleted or clarified. The beginning of the sentence could be clearer if it were to state: "Investigators should consider all aspects and types of relationships to be a potential financial interest, including…."
- 2.3: Change "financial conflict of interest" to "financial interest."

3. *IRB Members and Staff*

- 3.1: In the second sentence, it may be clearer if it were to state "deliberating **and** voting." A sentence should be added to the end of this section that would convey the

following information: Members who recuse themselves from participating in the review of a study in which they have a conflict of interest may not be counted toward the quorum necessary to transact business.

- 3.3: The first "policy" should have the "p" capitalized.

4. *IRB Review of Protocols and Approval of Consent Documents*

- General: As noted in the comments that follow, we believe that some of the items listed should be the responsibility of the COIC. As such, they should be moved from this section to the section on institutional responsibilities (Section 1).
- 4.1: It is the COIC that should determine how a financial interest should be eliminated or managed. The IRB should only consider whether risks to subjects need to be minimized (due to the financial interest)—which might include not allowing the study to be done at the institution—or whether information about the financial interest should be conveyed to subjects.
- 4.2: This is the first paragraph where the parenthetical phrase "(Institutionally based and non-Institutionally based)" is included. If this is meant as a way to establish the responsibilities of independent IRBs, it is not very helpful. We recommend that a separate section be added to this document specifically addressing our expectations with regard to research that is conducted in a private practitioners office under the purview of an independent IRB (a situation where no institution may exist). Further, we believe that it could compromise an IRB (and bring increased pressure to approve a study) if IRBs were to know all funding information for each protocol they review. Similarly, for the same reasons, the funding of the IRB is an administrative issue that should be kept separate from the IRB's review function. Rather 4.2 should place this responsibility on COICs (not IRBs).
- 4.3, 1st indented paragraph: It is the COIC that should consider all categories in the PHS and FDA requirements, not the IRB. Further, it is not helpful to simply reference these documents. If this guidance is to be helpful to all parties, the applicable information from the PHS and FDA regulations should be listed.
- 4.3, 2nd indented paragraph: It should be the responsibility of the COIC to consider "the answers to the following questions" that concern financial relationships rather than the IRB. In additional to asking whether there is a DSMB, one should also ask "what is the monitoring plan for the trial?" In the "Note", "COICs" should replace "IRB. It may also be reasonable to ask whether the investigator's immediate family may profit in some way.
- 4.4, 1st sentence: We suggest that the first part of this sentence should be modified to read: "IRBs should carefully consider the specific mechanisms implemented by the COIC to minimize the potential adverse consequences...."

5. *Consent*

- General: We believe that the institution should be cautioned about relying on the consent form as a way of managing financial interests. When financial interests are either appropriately managed or eliminated, there may be no need for any disclosure of this information to the subject. Disclosure of financial interests to subjects may cause to confuse rather than to inform the subject. While subjects may be interested

that a certain dollar amount is being provided for each subject enrolled, they are likely to be less interested in the source of funding.

- 5.1: We question whether the consent form should include the source of funding and funding arrangements for performing the IRB review of the protocol. What would this mean, for example, in an academic institution where the institution's business office requires a certain portion of the grant/contract to go to institutional overhead (including the IRB function)? If NCI were the sponsor, would this mean that NCI or the institution should be identified in the consent form as paying for the IRB review of that protocol? What meaning would that have to subjects? Could it cause them to have greater or lesser confidence in the IRB's review?
- 5.2: It is very difficult, without further guidance, to know what might be "material" to the subject's decision-making process. Please note the general comment above. If this were to be retained, some guidance on "materiality" would be helpful.

We hope these comments are useful to you. If you have any questions, please contact me.

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